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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
Patrick D. MIZE

SERIAL NO: 10/721,498 GROUP: 1654

FILED: November 26, 2003 EXAMINER: Louise N. LEARY

FOR: LOW MOLECULAR WEIGHT HEPARIN ASSAY AND REAGENTS THEREFOR

LETTER

Mail Stop DD
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith is an European Office Action for the Examiner's consideration. The reference(s) cited therein have been previously filed on November 26, 2003 and May 25, 2005.

Respectfully Submitted,

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Application No.	Ref.	Date
02 784 766.4 - 1212	SR25217 US/EE	22.07.2005
Applicant: Cardiovascular Diagnostics, Inc.		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

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Boiangiu, C
Primary Examiner
for the Examining Division

Enclosure(s): 6 page/s reasons (Form 2906)

Registered Letter
EPO Form 2001 07.02CSX

Bescheid/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
Datum Date Date 22.07.2005	Blatt Sheet Feuille 1	Anmelde-Nr.: Application No.: 02 784 766.4 Demande n°:

The examination is being carried out on the following application documents:

Description, Pages

2-18 as published

Claims, Numbers

1-26 as published

Drawings, Sheets

1/6-6/6 as published

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The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

11-26-03 Filed
Filed 5-25-05
Filed 5-25-05

D1:WO 01/44493 A (PENTAPHARM AG; GEMPELER, PATRICIA, MARIA; CALATZIS, ANDREAS) 21 June 2001 (2001-06-21)

D2:WO 99/10746 A (THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL; WU, HAI-FENG) 4 March 1999 (1999-03-04)

D3:WO 89/10788 A (CARDIOVASCULAR DIAGNOSTICS INC) 16 November 1989 (1989-11-16)

I. Documents disclosure:

D1 discloses: A hematological assay in which the blood coagulation potential of a body fluid is measured by reacting a sample of the body fluid with an amount of an activator reagent comprising a predetermined amount of **factor Xa** (or an activator of it). The concentration or presence of heparin or another anticoagulant is determined in a whole blood sample by correlating the clotting time with the heparin concentration (claim 36; from page 3, line 9 to page 4, line 14; from page 21, line 19 to page 22, line 17).

D2 discloses: A method for determining the concentration of low molecular weight heparin (especially Enoxaparin) or heparin in a blood plasma sample comprises the steps of adding a dilute thromboplastin (or tissue **factor**) solution to a blood plasma sample; and then measuring the time of clot formation in said blood plasma sample (abstract; from page 3, line

14 to page 5, line 19; claims 1).

D3 discloses: A method and apparatus for the measurement of clot formation times, clot dissolution times, or clotting parameters. This method performs these measurements by monitoring movement of magnetic particles incorporated in the sample being assayed, where the movement is induced by a magnetic field. An instrument for temperature control is also provided. The reaction volume contains a measured amount of a dry coagulation assay. Moreover, the method and apparatus of D3 can be also use for the heparin assay (from page 5, line 1 to page 10, line 8; page 33, lines 24-29; claims 4, 12, 19-22, 40-52, 57-60).

II. Inventive step

II.1. The present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of **claims 1, 13, 14, 17, 23 and 26** does not involve an inventive step in the sense of Article 56 EPC.

Document **D1** is the closest prior art (see disclosure above). **D2** could as well be the closest prior art.

D1 (see disclosure above) discloses a simple assay used to determine the LMWH concentration, based on the relationship between the clotting time reaction and the LMWH amount in a whole blood sample (abstract; claim 36; from page 3, line 9 to page 4, line 14; from page 21, line 19 to page 22, line 17). **D1** also teaches, that the coagulation can be activated using the factor Xa, or an activator of the factor Xa, wherein the factor Xa activator can be snake venom enzymes. A factor Va or factor V activator from purified Russell's viper venom can be also used (page 20, lines 6-9; from page 21, line 19 to page 22, line 17).

II.2. The additional technical feature of **claim 1** over **D1 (or D2)** is the fact that the clotting mixture contains magnetic particles distributed substantially homogeneously therethrough and wherein the mixture is subjected to (ia) an oscillating magnetic field or (ib) a moving permanent magnetic field or (ic) a combination of an oscillating magnetic field and a stationary permanent magnetic field or (id) a rotating magnetic field and by monitoring the movement induced in the magnetic particles by (ia) or (ib) or (ic) or (id) the coagulation reactions can be

measured.

The problem to be solved by the present invention may therefore be regarded as to provide a method, system and reagents for an accurate, quick and easy quantitative measure of LMWHs (especially of Enoxaparin) in the whole blood sample.
The solution to this problem can be found in the use of the coagulation cascade reaction and the monitoring of the coagulation times or kinetics, wherein the coagulation reagent is a dry format reagent comprising magnetic particles and a factor Xa activator, such as Russell's Viper venom. The coagulation assays are monitored by monitoring the movement of magnetic particles. The coagulation based assay in dry chemistry format permit to correlate the clotting time to the LMWH levels, and thus to determine the LMWH concentrations in the whole blood sample.

However, it is well known in the art that the coagulation based assay can be used in order to determine the LMWHs concentration (e.g. Enoxaparin) (e.g. document D2).

Moreover, all the technical features of **claim 1** not disclosed in **D1** (or **D2**) are disclosed in **D3** document, which relates to:
Method and apparatus for the measurement of clot formation times in a whole blood sample, (see **D3**: abstract and claim 7):
(i) combining a first, whole blood, component of the assay with a second component of the assay to form a resulting mixture, wherein said second component comprises a dry coagulation assay reagent arranged in a substantially flattened configuration and containing magnetic particles distributed substantially homogeneously there through and comprising an activator, and wherein said resulting mixture is subjected to (ia) an oscillating magnetic field or (ib) a moving permanent magnetic field or (ic) a combination of an oscillating magnetic field and a stationary permanent magnetic field or (id) a rotating magnetic field, whereby said combining of said first component with said second component substantially simultaneously initiates movement of said magnetic particles and a coagulation assay measurement (**D3**: claims 4-7); and
(ii) monitoring movement induced in said magnetic particles by (ia) or (ib) or (ic) or (id) to obtain said coagulation assay measurement (**D3**: claims 4 and 5).

Because document **D3** describes that the additional technical features solve the problem

posed, combining it with the methods, the systems and the kits of document **D1** is obvious for a person skilled in the art, therefore the subject-matter of **claims 1** does not involve an inventive step in the sense of Article 56 EPC.

II.3. All the technical features of **claims 13, 14, 17, 23 and 26** not disclosed in **D1** (or **D2**) are disclosed in **D3** document which further discloses:
(i) adding a whole blood sample to a sample well of an element comprising:
a channel structure defining the sample well and a reaction volume in fluid communication with each other, wherein said reaction volume is defined by an upper surface having attached thereto a reflectance layer, comprising a semipermeable matrix wherein said reaction volume contains a measured amount of at least one dry coagulation assay reagent arranged in a substantially flattened configuration and containing magnetic particles distributed substantially homogeneously there through, wherein a specific volume of said sample is drawn into said reaction volume by capillary action and contacts, together with said semipermeable layer, said reagent to thereby substantially simultaneously initiate a coagulation assay measurement (**D3**: claims 4-7,12,14,19); and
(ii) performing said coagulation assay measurement by measurement the reflectance of said semipermeable layer (**D3**: figures 12, 30 and 34; from page 92 line 17 to page 93 line 14; from page 95 line 15 to page 96 line 9),
and
(i) an instrument with a means for temperature control, a means for producing an oscillating magnetic field or for moving a permanent magnetic field, an illuminating means, and a photometric monitoring means (**D3**: claim 42); and (ii) an element for performing said measuring, said element comprising a channel structure defining a sample well and reaction volume in fluid communication with each other, said channel structure having a geometry causing a liquid sample placed in said sample well to be drawn into and filling said reaction volume via capillary action, said reaction volume comprising at least one dry coagulation assay reagent arranged in a substantially flattened configuration and containing magnetic particles distributed substantially homogeneously there through (**D3**: claims 5, 12-14, 42).
and
(i) a reaction element comprising (1) a sample well for receiving a liquid sample and (2) a reaction chamber containing a dry coagulation assay reagent arranged in a substantially flattened configuration and in which is embedded, substantially homogeneously there through, magnetic particles (**D3**: claims 3 and 12);

(ii) said sample well and said reaction chamber being in fluid communication through a transport zone of geometry such that a volume of liquid sample placed in said sample well and corresponding to the volume of said reaction chamber is transported from said sample well to said reaction chamber simultaneously (**D3**: from page 97 line 19 to page 98 line 30);
(iii) means for optically monitoring said reaction chamber (**D3**: from page 97, line 19 to page 98, line 30);
(iv) means for subjecting said reaction chamber to an oscillating magnetic field (**D3**: claim 12);
(v) whereby, when said sample is introduced into said reaction chamber, said dry coagulation assay reagent is solubilized and said magnetic particles are thereby freed to move in an oscillating pattern induced by said oscillating magnetic field, thus providing a measurement of the kinetics of said coagulation assay corresponding to changes in the degree of said magnetic particles movement relative to said oscillating magnetic field... (**D3**: claim 4; from page 83, line 21 to page 84 line 14; example 1, from page 99, line 31 to page 100, line 3).

Therefore, the same reasoning as for the claim 1 can be applied *mutatis mutandis* to the independent **claims 13, 14, 17, 23 and 26**. Therefore, the subject-matter of **claims 13, 14, 17, 23 and 26** does not involve an inventive step in the sens of Article 56 EPC.

The subject-matter of dependent **claims 2-12, 15, 16, 18-22, 24 and 25** are well known in the art (see **D1-D3**) or merely add routine modification options to the subject-matter of **claims 1, 13, 14, 17, 23 and 26** and is therefore obvious to a person skilled in the art. For this reason the subject-matter of **claims 2-12, 15, 16, 18-22, 24 and 25** does not involve an inventive step in the sense of Article 56 EPC either.

III. Clarity

The relative terms "substantially" used in **claims 1, 13, 14, 17, 23** and **26** have no well-recognised meaning and leave the reader in doubt as to the meaning of the technical features to which they refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 84 EPC.

IV . Conclusion

It is not at present apparent which part of the application could serve as a basis for a new,

allowable claim. Should the applicant nevertheless regard some particular matter as patentable, independent claims should be filed taking account of Rule 29(1) and (2) EPC. The applicant should also indicate in the letter of reply the difference of the subject-matter of the new claim vis-à-vis the state of the art (D1-D3) and the significance thereof.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.